PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1667 WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/008389	International filing date *(day/month/year)* 11.03.2005	Priority date *(day/month/year)* 11.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K49/04 A61P43/00		
Applicant MALLINCKRODT INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.06.2006	04.10.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer GONZALEZ RAMON, N Telephone No. +31 70 340-3466

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/008389

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-17 as originally filed

   Claims, Numbers

   1-26 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-26 in part

because:

☒ the said international application, or the said claims Nos. 23-26 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1-26 in part

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,14,16-18,24,25
	No:	Claims	1,3-13,15,19-23,26
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	23-26 see separate sheet

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 23-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Present claims 1-26 relate to compounds defined by reference to vague characteristics or properties, namely: "alkoxy, hydroxyalkoxy", "alkyl residue", "cyclic residue", "being optionally interrupted by", "a carbohydrate" (claim 1); "aqueous buffer solutions", "balanced ionic solutions", "other non-radioactive additives" (claim 19); "a contrast agent other than the monomer and the dimer" (claim 21). In fact, the claims contain so many options, variables and possible permutations that a lack of clarity within the meaning of Article 6 PCT arises.

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Moreover, claims 19, 21, 22 encompass a genus of compounds defined only by their function "chelating agents" (claim 19); "a contrast agent" (claim 20); "X-ray contrast agent", "magnetic resonance imaging agent", "radionuclide imaging agent", "ultrasound imaging

agent", "optical imaging agent" (claim 22) wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.
Therefore, claims 1-26 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Support is only to be found in the present application for those parts relating to the compounds effectively disclosed in the examples and those specifically mentioned by chemical name in claims 15-18, 24, 25 and as such has been the subject of the search.

No opinion will be formulated by the ISA in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 23-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following documents (D) are referred to in this communication:

D1 : DE 196 27 309 A1 (SCHERING AG, 13353 BERLIN, DE) 8 January 1998.
D2 : EP 0 074 309 A (SOCIETE DITE: GUERBET S.A) 16 March 1983.
D3 : WO 94/14478 A (DIBRA S.P.A; BRACCO S.P.A; FELDER, ERNST; DE HAEN, CHRISTOPH) 7 July 1994.
D4: SOVAK M. ET AL: INVESTIGATIVE RADIOLOGY, vol. 39, no. 3, March 2004 (2004-03), pages 171-181, XP008062184
D5: WO 93/10825 A (MALLINCKRODT MEDICAL, INC) 10 June 1993 (1993-06-10)

Novelty (Art 33 (2) PCT)

The subject-matter of claims 1, 3-13, 15, 19-23, 26 is not new in the sense of Article 33(2) PCT. The reasons therefore are the following:

D2 discloses opacifying compositions for radiography comprising a mixture of two or more of compounds of formulae Ib and Ic embraced by present formula I **when X is I** and compounds of formulae IIb and IIc embraced by present formula II **when X is I** (see pages 11-14). Their use in the form of injectable preparation is also described (see page 52, lines 20-30).
Therefore rendering the subject matter of present claims 1, 3-13, 15, 19-23, 26 not novel.

D3 discloses an aqueous injectable formulation for radio diagnosis comprising a mixture of iodinated aromatic compounds constituted by a) a triiodo substituted monoaromatic nucleus embraced by present formula I and including iopamidol, iopromide, ioversol, iohexol, iopentol and b) compounds comprising at least two triiodo substituted aromatic of formula (II) embraced by present formula II wherein substituents A, B, D are -CON(R)R1 or -N(R)-CO-R2 being R=H . Optionally comprising other opacifying compounds of three or more polyiodinated aromatic nuclei (see page 1, lines 4-20; tables 2, 3)
Consequently the subject matter of claims 1, 3-13, 15, 19-23, 26 is not new over D3.

Inventive step (Art 33(3) PCT)

Should the applicant overcome the above raised objections, an inventive step has to be demonstrated for the subject matter of present claims 1-26 (Art 33(3) PCT).

According to the description (page 2, lines 1-4), the problem underlying the present invention is the undesirable physiologic adverse reaction to X-ray contrast media, e. g., nausea, vomiting, heat and pain.

As solution to this problem a composition comprising a mixture of a triiodinated monomer corresponding to formula I as depicted in claim 1 and a dimer corresponding to formula II as depicted in claim 1 is proposed.

Previously discussed document D3 discloses the invention as present on file and therefore the subject matter of present claims 1, 3-13, 15, 19-23, 26 is obvious for the skilled person in view of D3.

The difference between D3 and the subject matter of present claims 2, 12, 16-18 is the fact that the particular triiodinated aromatic compounds as in present claims 2, 12 is not explicitly disclosed in D2 as well as the use of the specific combinations with iosmin (namely iosimenol) claimed by present claims 16-18.

D5 discloses Triiodinated isophthalamide derivatives embraced by present formulae I and II as X-ray contrast agents (see page 6, line 20- page 7, line 6; claims 18-21)

Consequently the use of these alternative non-ionic triiodinated contrast agent in the claimed composition is rendered obvious to the skilled person in view of D5.

Furthermore the skilled person would have been further reinforced in his choice of the compounds of D3 as suitable alternatives by the teaching of D4 stating that iosimenol, the a low-viscosity non ionic dimer pharmacologic characteristics closely resemble those of iotrolan and iodixanol compounds used in D3 (see conclusions).

Furthermore, the attention of the applicant is also drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step.
When the inventive step is solely based on the achievement of a technical effect, such as

to overcome the undesirable physiologic adverse reaction to X-ray contrast media, e. g., nausea, vomiting, heat and pain, substantially all embodiments should exhibit this effect.

However, it is evident that the number of compositions/compounds comprising groups encompassed under "alkoxy, hydroxyalkoxy", "alkyl residue", "cyclic residue", "being optionally interrupted by", "a carbohydrate" (claim 1); "aqueous buffer solutions", "balanced ionic solutions", "other non-radioactive additives" (claim 19); "chelating agents" (claim 19); "a contrast agent" (claim 20); "a contrast agent other than the monomer and the dimer" (claim 21); "X-ray contrast agent", "magnetic resonance imaging agent", "radionuclide imaging agent", "ultrasound imaging agent", "optical imaging agent" (claim 22) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-26 does not exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Consequently an inventive step for the subject matter of claims 1-26 cannot be acknowledged.